PANEL MEMORANDUM

TO: **Panel Members**

FROM: Samie Allen, ODE/DGRND/PRSB

DATE: June 5, 2002

SUBJ: P990074
Inamed (formerly McGhan Medical)
McGhan Saline-Filled Breast Implants
Status of PMA Conditions of Approval

Background:

On May 10, 2000, the McGhan RTV Saline-Filled Breast Implants were approved for females for the following indications:

- ?? Breast Augmentation. A woman must be at least 18 years old for breast augmentation.
- ?? Breast Reconstruction.

There were 5 conditions of approval for this PMA:

1. Post-approval study
2. Focus group study
3. Retrieval study
4. Fatigue testing
5. Shelf life testing

The status of each condition of approval is presented below.

1. Post-Approval Study

The purpose of the post-approval study is to collect additional safety data out to 10 years on patients already enrolled in the Augmentation 95 (A95) and Reconstruction 95 (R95) prospective clinical studies. Inamed referred to their post-approval study as the Post-Approval Survey Study (PASS). The PASS is, by Inamed's choice, a 2-phase study with (1) patients followed out to 5 years as per the original protocol of A95/R95 followed by (2) patients followed as per the abbreviated protocol from 6-10 years. Inamed provided all available 5-year data, collected as per the original protocol of A95 and R95, in a 2001 annual report. The date of database closure is 8/15/01.

The A95 Study data are presented first, followed by the R95 Study data.

AUGMENTATION – A95 STUDY RESULTS

There were a total of 913 patients originally enrolled in the study, with 12 patients excluded from the analysis because they did not meet the inclusion/exclusion criteria -- 8 patients for pre-existing CTD diagnosis, 1 for pregnancy, 1 for informed consent after surgery, 1 for implantation with non-study devices, and 1 with prior implants -- making 901 the number of patients (1800 implants) reported in this study. Patients were discontinued from the study for the following conditions: death, removal of all originally implanted implants, and patient choice. The patient disposition at 5 years for the A95 study is summarized in Table 1 below. The 5-year follow-up rate (defined as actual divided by expected) is estimated to be 81.1%, which is an acceptable follow-up rate.

Table 1: Patient disposition at 5 years on a by patient basis - A95

N = 901 Patients Enrolled[1] N = 1800 Devices Implanted	
Theoretical Follow-up N = 901 Expected Follow-up[2] N = 846 Actual Follow-up N = 686 Percent Follow-up[3] = 81.1%	
Withdrawals N = 215	
Reason for Withdrawal	Number of Patients Withdrawn
Deaths[4]	N = 1
Implant Removal[5]	N = 54
Lost to Follow-up	N = 160

Notes: [1]Excludes 12 patients who did not meet the inclusion/exclusion criteria.
[2]Expected follow-up is theoretical follow-up minus deaths and removals of all originally implanted devices.
[3]Defined as actual divided by expected follow-up.
[4]The patient had pre-existing gestational diabetes and died of a ruptured aneurysm approximately 2½ years after implantation, reporting several complications -- asymmetry, breast pain, loss of nipple sensation, skin paresthesia/hypersensitivity, and implant wrinkling -- none of which were rated as severe or very severe.
[5]Defined as removal of all primary study implants prior to the study interval.

Table 2 below summarizes the 3 and 5-year cumulative Kaplan Meier risk rates of first occurrence of complications in ?1% frequency, reported on a by-patient basis. Note that the complications of delayed wound healing, implant extrusion, lymphadenopathy, pneumothorax, and tissue/skin necrosis were all at a risk rate of <1% and are omitted from this table. Although the by-implant rates are slightly lower than the by-patient basis rates, only the by-patient rates are included here because this is the presentation reported in the patient labeling for this product.

Although comparison of the 3-year and 5-year rates show higher rates at 5 years compared to at 3 years, because the confidence intervals are overlapping, the true rate may not be higher, with the exception of implant removal. ***For implant removal, the confidence intervals at 3 years and at 5 years do not overlap, indicating potentially significantly higher rates at 5 compared to 3 years. It would be reasonable to suggest, based on these data, that implant removal, at minimum, be followed for prolonged periods of time (perhaps indefinitely), given that the risk rate appears to be changing over time, that it is an objective and easily measured endpoint, and that the time at which this event occurs can be more precisely determined rather than estimated.***

Table 2: By patient cumulative Kaplan-Meier risk rate of first occurrence (95% confidence interval) of complications occurring in ?1% at 3 and 5 years of follow-up - A95.

Kaplan-Meier Risk Rates	**3-Year Risk Rate[1] N = 901**		**3-Year Risk Rate[2] N = 901**		**5-Year Risk Rate N = 901**	
Complication	**Rate**	**95% CI**	**Rate**	**95% CI**	**Rate**	**95% CI**
Reoperation	21.1%	(18.4, 23.8)	21.4%	(18.7, 24.1)	25.9%	(23.0, 28.9)
Breast Pain[3]	15.6%	(13.2, 17.9)	15.9%	(13.5, 18.4)	17.0%	(14.5, 19.5)
Wrinkling[3]	10.5%	(8.4, 12.6)	10.6%	(8.6, 12.7)	13.7%	(11.3, 16.1)
Asymmetry[3]	10.1%	(8.1, 12.1)	10.3%	(8.2, 12.3)	12.2%	(10.0, 14.4)
Palpability/Visibility[3]	9.2%	(7.2, 11.1)	9.6%	(7.6, 11.6)	12.1%	(9.8, 14.3)
Implant Removal	7.6%	(5.8, 9.4)	7.7%	(6.0, 9.5)	11.8%	(9.6, 14.0)
Capsular Contracture[4]	8.7%	(6.8, 10.6)	8.8%	(6.9, 10.6)	11.4%	(9.2, 13.5)
Loss of Nipple Sensation[3]	8.4%	(6.5, 10.2)	8.3%	(6.5, 10.2)	9.9%	(7.8, 11.9)
Nipple Paresthesia[3]	9.3%	(7.4, 11.2)	9.3%	(7.4, 11.2)	9.8%	(7.8, 11.8)
Implant Malposition[3]	8.2%	(6.3, 10.0)	8.1%	(6.3, 10.0)	9.2%	(7.3, 11.2)
Skin Paresthesia[3]	7.2%	(5.5, 9.0)	7.2%	(5.5, 8.9)	7.6%	(5.9, 9.4)
Leakage/Deflation	5.0%	(3.5, 6.4)	4.5%	(3.1, 5.9)	6.8%	(5.0, 8.5)
Scarring	6.4%	(4.8, 8.0)	6.4%	(4.7, 8.0)	6.5%	(4.9, 8.2)
Irritation/Inflammation[3]	2.9%	(1.8, 4.0)	3.0%	(1.9, 4.2)	3.2%	(2.0, 4.3)
Seroma	2.6%	(1.6, 3.7)	2.6%	(1.6, 3.7)	2.6%	(1.6, 3.7)
Skin Rash	1.6%	(0.8, 2.4)	1.6%	(0.8, 2.4)	1.9%	(1.0, 2.8)
Capsule Calcification[3]	1.2%	(0.4, 1.9)	1.4%	(0.6, 2.2)	1.8%	(0.9, 2.7)
Hematoma	1.7%	(0.7, 2.4)	1.7%	(0.8, 2.5)	1.7%	(0.8, 2.5)
Delayed Wound Healing[3]	<1%	<1	0.7%	(0.1, 1.2)	0.8%	(0.2, 1.4)
Infection	<1%	<1	0.7%	(0.1, 1.2)	1.0%	(0.3, 1.6)

Notes: [1]3-year data as reported in original PMA.
[2]Updated 3-year data as reported in 2001 annual report. Differences from original PMA data are minor.
[3]Includes only reports of moderate, severe, or very severe. Reports of very mild and mild are excluded.
[4]Includes Baker Grade III or IV. If a Baker Grade was not given but either capsular contracture was reported specifically or a capsule treatment was performed and firmness was reported, Baker Grade was assumed to be Grade IV.

With respect to **additional surgical procedures**, there were a total of 463 additional surgical procedures performed at 293 reoperations (additional operations) in 224 of the 901 patients over the 5 years of follow-up in the augmentation patients. Of the 224 patients undergoing reoperation, the majority (184 patients, 82%) underwent one reoperation, 26 patients (12%) underwent 2 reoperations, and 14 patients (6%) underwent 3 or more reoperations. The types of reoperations performed through 5 years -- and through 4 years as reported in the original PMA submission -- is summarized in Table 3 below. Inamed reported 61 additional procedures through 5 years than reported from the 4-year data in the original PMA. The types and frequency of procedures were similar between these years. **Through both 4 and 5 years, implant removal with replacement was the most commonly performed surgical procedure -- constituting approximately one-third of the procedures -- followed by capsulotomy, saline adjustment, scar/wound revision, aspiration, and mastopexy.**

Table 3: Types of additional surgical procedures performed through 4 and 5 years - A95

Type of Procedure	**4 Years[1] N = 402 Procedures**	**5 Years N = 463 Procedures**
Removal with Replacement	122 (30.3%)	156 (33.7%)
Capsule Procedure	78[2] (19.4%)	86[3] (18.6%)
Adjust Saline Fill	46 (11.4%)	49 (10.6%)
Scar Revision/Wound Repair	33 (8.2%)	40 (8.6%)
Aspiration	28 (7.0%)	29 (6.3%)
Mastopexy	28 (7.0%)	28 (6.0%)
Biopsy/Lump Removal	16 (4.0%)	21 (4.5%)
Implant Reposition	19 (4.7%)	20 (4.3%)
Removal without Replacement	10 (2.5%)	10 (2.2%)
Skin Lesion/Cyst Removal	6 (1.5%)	10 (2.2%)
Other	7[4] (1.7%)	7[5] (1.5%)
Exploration of Breast Area/Implants	8 (2.0%)	6 (1.3%)
Nipple Related	1 (0.2%)	1 (0.2%)

Notes: [1]As reported in original PMA submission with recategorization of several "other" procedures. No new data were added. N of 402 remains the same.

[2]Includes capsulotomy (57 cases), capsulectomy (12 cases), and capsulorraphy (9 cases).

[3]Includes capsulotomy (63 cases), capsulectomy (12 cases), and capsulorraphy (11 cases).

[4]Includes laser pigmentation increase (4 cases), excision of excess skin (2 cases), and relaxing incisions (1 case).

[5]Includes: laser pigmentation increase (2 cases), excision of excess skin (2 cases), relaxing incisions (1 case) and revision of plication pocket (2 cases). Values at 5 years are less than at 4 years due to further clarification of the type of surgical procedure performed and/or data cleaning.

Of the 1800 augmentation implants, there were 166 **implant removals** (9.2%) through 5 years for any reason. Of the 166 implant removals, 96 (57.8%) were removed due to a complication (see Table 4 below for the primary reason for implant removal), and the majority (156 of 166 implants, 94.0%) were replaced. Of the 901 patients, there were 98 patients who had an implant removed (10.9%). For comparison, at 4 years, 132 (7.3%) implants were removed, with 75 (56.8%) implants removed due to a complication and 122 (92.4%) implants replaced. Of the 901 patients, 81 (9.0%) patients had an implant removed through 4 years.

Table 4: Primary reason for implant removal through 4 and 5 years - A95.

Primary Reason for Removal[1]	**4 Years**[2] **N = 132 Implants Removed**	**5 Years N = 166 Implants Removed**
Patient Choice	57[3] (43.2%)	70[4] (42.2%)
Leakage/Deflation	44 (33.3%)	54[5] (32.5%)
Capsular Contracture	13[6] (9.8%)	17[6] (10.2%)
Wrinkling/Asymmetry/Malposition	10[7] (7.6%)	9[8] (5.4%)
Implant Palpability/Visibility	0 (0.0%)	6 (3.6%)
Other	2[9] (1.5%)	4[10] (2.4%)
Breast Pain	3 (2.3%)	3 (1.8%)
Implant Extrusion	1 (0.8%)	1 (0.6%)
Infection	1 (0.8%)	1 (0.6%)
Iatrogenic Injury	1 (0.8%)	1 (0.6%)

Notes: [1]In the case where more than one reason for removal is reported, the following hierarchy is used to determine the primary reason: leakage/deflation, infection, implant extrusion, capsular contracture, implant wrinkling, implant palpability/visibility, implant malposition, asymmetry, hematoma, breast pain, iatrogenic injury, patient choice to change size/style or to match other side.
[2]As reported in original PMA submission with categorization of "unknown" primary reason for removal No new data were added. N of 132 remains the same.
[3]Includes change size/style (53 cases), media-related anxiety (2 cases), and match other side (2 cases).
[4]Includes change size/style (64 cases), media-related anxiety (2 cases), and match other side (4 cases).
[5]Includes 1 case of "Unknown" as a worst case presentation.
[6]Includes 1 case of capsular contracture "baker II".
[7]Includes wrinkling (6 cases) and asymmetry (4 cases).
[8]Includes wrinkling (6 cases) and asymmetry (3 cases). Values at 5 years are less than at 4 years due to further clarification of the primary reason for removal and/or data cleaning.
[9]Includes "too much upper pole fullness" (2 cases)
[10]Includes "too much upper pole fullness" (2 cases) and "to be smaller, treat ptosis" (2 cases).

For those patients who underwent **implant revision** (removal with replacement) and had follow-up, the complications of capsular contracture grade III/IV, leakage/deflation, removal, and infection **following implant revision** is summarized in Table 5 below on a by implant basis through 2 and 3 years.

Table 5: Cumulative Kaplan-Meier risk rates of first occurrence of selected complications on a by-implant basis following implant replacement (revision) at 2 and 3 years - A95.

Complication Following Replacement (Revision)	**2-Year Risk Rate**[1] **(95% CI) N = 108 Implants**	**2-Year Risk Rate**[2] **(95% CI) N = 126 Implants**	**3-Year Risk Rate (95% CI) N = 126 Implants**
Removal/Replacement	5.4% (0.2, 10.5)	5.3% (0.7, 9.8)	18.3% (9.4, 27.1)
Leakage/Deflation	9.1% (3.4, 14.7)	5.8% (1.6, 10.0)	9.3% (3.1, 15.6)
Capsular Contracture III/IV	7.3% (1.5, 13.0)	7.6% (2.5, 12.7)	7.6% (2.5, 12.7)
Infection	1.0% (0.0, 3.0)	2.5% (0.0, 5.3)	2.5% (0.0, 5.3)

Notes: [1]As reported in original PMA submission.
[2]Updated 2-year data as reported in 2001 annual report.

With respect to **breast disease**, there were 81 patients of 901 (9.0%) who reported breast disease through 5 years of follow-up. Of these 81 reports, 80 were benign (most commonly breast mass/lump or fibrocystic disease) and 1 was malignant (unilateral carcinoma in a bilaterally implanted woman, diagnosed 27 months after implantation). For comparison, as reported in the original PMA submission, there were 54 reports of breast disease through 4 years (44 benign, 1 malignant, and 9 unknown). However, in the 2001 annual report, Inamed indicated that there were 22 additional reports of benign breast disease which were inadvertently omitted from the original PMA submission, bringing the overall count of benign breast disease to 66 reports through 4 years. Additionally, since year 4, 2 reports of breast disease with unknown outcome were determined to be false reports and were removed and the remaining 7 reports of breast disease with unknown outcome at year 4 were recategorized to benign. Therefore, of the 81 reports of breast disease through 5 years, 7 are actually new reports from year 4.

With respect to **Connective Tissue Disease (CTD)**, there were a total of 20 patients reporting a CTD through 5 years of follow-up. Of these 20 reports, 7 were confirmed (3 Graves' disease, 2 hyperthyroiditis, and 2 chronic fatigue syndrome or fibromyalgia—CF/FM). 13 of these 20 reports were unconfirmed (4 thyroiditis, 1 inflammatory bowel disease, 1 hyperthyroiditis, 1 lupus or rheumatoid arthritis (RA), 4 CF/FM, 1 seronegative spondylarthritis, and 1 combination Graves' disease, Hyperthyroiditis, Raynaud's phenomenon, and RA). For comparison, as reported in the original PMA submission, there were 12 reports of CTD, 5 confirmed and 7 unconfirmed, through 4 years. The number of confirmed reports has increased from 5 reports at 4 years to 7 reports at 5 years due to 2 new confirmed reports (1 Graves' disease and 1 hyperthyroiditis). The number of unconfirmed reports has increased from 7 reports at 4 years to 13 reports at 5 years due to the addition of 9 new unconfirmed reports (1 inflammatory bowel disease, 3 thyroiditis, 4 CF/FM, and 1 seronegative spondylarthritis) and the deletion of 3 unconfirmed reports that were found to be false reports (2 lupus or RA and 1 thyroiditis). Additionally, 1 patient reported with an unconfirmed diagnosis of hyperthyroiditis at 4 years was reclassified to an unconfirmed diagnosis of hyperthyroiditis, RA, Graves' disease, and Raynaud's phenomenon. Therefore, of the 20 patients reporting CTD through five years, 11 are actually new reports (2 confirmed, 9 unconfirmed) from year 4.

There have been reports in the literature[1,2,3,4] that CF/FM may be more prevalent in patients with breast implants. If both confirmed and unconfirmed reports of CF/FM are included, the incidence of CF/FM in the A95 population is 6 of 901 patients (0.7%), which is lower than the incidence of 1-4% reported[5] for industrialized countries. If all the confirmed and unconfirmed CTD's reported in the A95 are combined, the prevalence of 20 of 901 patients (2.2%) reported in this study is also lower than combined incidence of CTD reported in the general female population, which generally excludes thyroid disease. However, it is not clear to what degree ascertainment bias in the A95 study is relevant, in that it is unknown how many patients who were complaining of rheumatic signs/symptoms and were referred for a rheumatologic diagnostic work-up actually underwent a formal evaluation by a Rheumatologist. Note that thyroiditis/Grave's disease is a frequent report in the A95 study. This is not surprising given that they are relatively common disorders, are especially common in the third and fourth decades, and are more common in women (Grave's disease, for example has a 7:1 female:male prevalence).

[1] Wolf F. Silicone related symptoms are common in patients with fibromyalgia: no evidence for a new disease. J Rheum 1999; 26:1172-1175.
[2] Cuellar ML, et.al. Silicone breast implant-associated musculoskeletal manifestations. Clin Rheumatol 1995; 14: 667-672.
[3] Peters, W, et.al. An outcome analysis of 100 women after explantation of silicone gel breast implants. Ann Plast Surg 1997; 39:9-19.
[4] Brown SL, et.al. Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women. J Rheum 2001; 28: 992-1003.
[5] Wolfe F, et.al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995; 38: 19-28.

RECONSTRUCTION – R95 STUDY RESULTS

There were a total of 256 patients originally implanted in the study, with 19 patients excluded from the analysis because they did not meet the inclusion/exclusion criteria -- 12 patients for a pre-existing CTD diagnosis, 3 for a having a previous breast implant, 2 for use of non-study devices, 1 for a congenital deformity, and 1 for informed consent after surgery -- making 237 the number of patients (316 implants) reported in this study. The patient disposition at 5 years for the R95 study patients is summarized in Table 6 below. The 5 year follow-up rate (defined as actual divided by expected) is estimated to be 80%, which is an acceptable follow-up rate.

Table 6: Patient disposition at 5 years on a by patient basis - R95

N = 237 Patients Enrolled[1] N = 316 Devices Implanted	
Theoretical Follow-up N = 237 Expected Follow-up[2] N = 175 Actual Follow-up N = 140 Percent Follow-up[3] = 80%	
Withdrawals N = 97	
Reason for Withdrawal	Number of Patients Withdrawn
Deaths[4]	N = 11
Implant Removal[5]	N= 51
Lost to Follow-up	N = 35

Notes: [1]Excludes 19 patients who did not meet the inclusion/exclusion criteria.
[2]Expected follow-up is theoretical follow-up minus deaths and removals of all originally implanted devices.
[3]Defined as actual divided by expected follow-up.
[4]1 due to breast cancer, 7 due to metastatic cancer, 1 due to complications associated with chemotherapy, 1 due to asphyxiation due to aspiration, and 1 due to unknown causes.
[5]Defined as removal of all primary study implants prior to the study interval.

Table 7 below summarizes the 3 and 5-year cumulative **Kaplan-Meier risk rates** of first occurrence of complications in ?1% frequency, reported on a by-patient basis. Note that the complications of lymphadenopathy, nipple paresthesia, and pneumothorax were all at rates below 1% and are omitted from this table. Although the by-implant rates are lower than the by-patient rates, for brevity, only by-patient rates are included because this is the presentation that is reported in the patient labeling for the product. Although comparison of the 3-year and 5-year rates show higher rates at 5 years compared to at 3 years, because the confidence intervals are overlapping, the true rate may not be higher.

Table 7: By patient cumulative Kaplan-Meier risk rate of first occurrence (95% confidence interval) of complications occurring in ? 1% at 3 years and 5 years of follow-up - R95.

Kaplan-Meier Risk Rates	**3-Year Risk Rate[1] N = 237**		**3-Year Risk Rate[2] N = 237**		**5-Year Risk Rate N = 237**	
Complication	**Rate**	**95% CI**	**Rate**	**95% CI**	**Rate**	**95% CI**
Reoperation	38.7%	(32.3, 45.0)	39.1%	(32.7, 45.4)	44.5%	(37.9, 51.0)
Asymmetry[3]	33.0%	(26.6, 39.4)	32.9%	(26.5, 39.3)	39.0%	(32.1, 45.8)
Capsular Contracture[4]	25.3%	(19.5, 31.2)	25.3%	(19.5, 31.1)	35.7%	(29.0, 42.4)
Implant Removal	22.5%	(17.1, 28.0)	22.5%	(17.0, 27.9)	28.0%	(22.1, 34.0)
Palpability/Visibility[3]	20.0%	(14.5, 25.5)	20.0%	(14.5, 25.5)	27.1%	(20.6, 33.5)
Wrinkling[3]	23.3%	(17.5, 29.1)	23.3%	(17.5, 29.2)	24.6%	(18.6, 30.6)
Loss of Nipple Sensation[3]	12.0%	(7.4, 16.6)	11.9%	(7.3, 16.6)	18.1%	(12.5, 23.8)
Breast Pain[3]	15.3%	(10.3, 20.2)	15.3%	(10.4, 20.2)	17.7%	(12.4, 23.0)
Implant Malposition[3]	12.2%	(7.8, 16.6	12.7%	(8.2, 17.2)	16.9%	(11.7, 22.2)
Leakage/Deflation	6.2%	(2.9, 9.5)	6.2%	(2.9, 9.5)	7.5%	(3.8, 11.2)
Irritation/Inflammation[3]	6.6%	(3.3, 9.8)	6.6%	(3.3, 9.8)	6.6%	(3.3, 9.8)
Skin Paresthesia[3]	5.6%	(2.5, 8.6)	5.6%	(2.5, 8.6)	6.3%	(2.9, 9.6)
Scarring	6.0%	(2.7, 9.2)	6.0%	(2.7, 9.2)	6.0%	(2.7, 9.2)
Infection	4.8%	(2.0, 7.5)	5.3%	(2.4, 8.2)	6.0%	(2.8, 9.2)
Capsule Calcification[3]	4.7%	(1.9, 7.6)	4.7%	(1.9, 7.6)	5.4%	(2.3, 8.6)
Seroma	3.9%	(1.4, 6.4)	3.9%	(1.4, 6.4)	3.9%	(1.4, 6.4)
Tissue/Skin Necrosis	3.6%	(1.1, 6.0)	3.6%	(1.1, 6.0)	3.6%	(1.1, 6.0)
Skin Rash	3.3%	(0.9, 5.7)	3.3%	(0.9, 5.7)	3.3%	(0.9, 5.7)
Implant Extrusion	2.6%	(0.6, 4.7)	2.6%	(0.6, 4.7)	3.2%	(0.9, 5.6)
Delayed Wound Healing[3]	2.7%	(0.6, 4.9)	2.7%	(0.6, 4.9)	2.7%	(0.6, 4.9)
Hematoma	1.3%	(0.0, 2.8)	1.3%	(0.0, 2.8)	1.3%	(0.0, 2.8)

Notes: [1]3-year data as reported in original PMA.
[2]Updated 3-year data as reported in 2001 annual report. Differences from original PMA data are minor.
[3]Includes only reports of moderate, severe, or very severe. Reports of very mild and mild are excluded.
[4]Includes Baker Grade III or IV. If a Baker Grade was not given but either capsular contracture was reported specifically or a capsule treatment was performed and firmness was reported, Baker Grade was assumed to be IV.

With respect to **additional surgical procedures**, there were a total of 159 additional surgical procedures performed at 126 reoperations in 100 of the 237 patients over the 5 years of follow-up in the reconstruction patients. Of the 100 patients undergoing reoperation, the majority (81 patients, 81.0%) underwent one reoperation, 13 patients (13%) underwent 2 reoperations, and 6 patients (6%) underwent 3 or more reoperations. The types of reoperations performed through 5 years -- and through 4 years as reported in the original PMA submission -- is summarized in Table 8 below. Inamed reported 8 additional procedures through 5 years than reported from the 4-year data in the original PMA. Note that planned procedures, such as subsequent but planned nipple reconstruction and nipple tattoo, were excluded from these values. **Implant removal with replacement was the most commonly performed procedure for both through years 4 and 5 -- constituting approximately one-third of the procedures -- followed by scar revision/wound repair, removal without replacement, capsule procedure, saline adjustment, biopsy/lump removal, aspiration, and implant reposition through 5 years.**

Table 8: Types of additional surgical procedures performed through 4 and 5 years - R95.

Type of Procedure (excluding planned procedures)	**4 Years[1] N = 151 Procedures**	**5 Years N = 159 Procedures**
Removal with Replacement	45 (29.8%)	49 (30.8%)
Scar Revision/Wound Repair	27[2] (17.9%)	28[3] (17.6%)
Removal without Replacement	17 (11.3%)	21 (13.2%)
Capsule Procedure	18[4] (11.9%)	13[5] (8.2%)
Adjust Saline Fill	9 (6.0%)	10 (6.3%)
Other	11[6] (7.3%)	11[7] (6.9%)
Aspiration	7 (4.6%)	7 (4.4%)
Biopsy/Lump Removal	7 (4.6%)	7 (4.4%)
Implant Reposition	6 (4.0%)	7 (4.4%)
Unplanned Nipple Procedure	3 (2.0%)	3 (1.9%)
Skin Lesion/Cyst Removal	1 (0.7%)	3 (1.9%)

Notes: [1]As reported in original PMA submission with recategorization of several "other" procedures. No new data were added. N of 151 remains the same.

[2]Includes flap revision (4 cases), crease revision/reconstruction (3 cases), scar revision (14 cases), and wound repair (6 cases).

[3]Includes flap revision (3 cases), crease revision/reconstruction (5 cases), scar revision (14 cases), and wound repair (6 cases). Values at 5 years are less than at 4 years due to further clarification of the type of surgical procedure performed and/or data cleaning.

[4]Includes capsulotomy (7 cases), capsulectomy (8 cases), and capsulorraphy (3 cases).

[5]Includes capsulotomy (5 cases), capsulectomy (5 cases), and capsulorraphy (3 cases). Values at 5 years are less than at 4 years due to further clarification of the type of surgical procedure performed and/or data cleaning.

[6]Includes excision of excess skin (6 cases), revise lateral left breast (1 case), liposuction procedures (2 cases), and placement of stacked implant (2 cases).

[7]Includes excision of excess skin (6 cases), revise lateral left breast (1 case), axillary liposuction (1 case), placement of stacked implant (1 case), TRAM flap (1 case), and chest wall liposuction (1 case). Values at 5 years are less than at 4 years due to further clarification of the type of surgical procedure performed and/or data cleaning.

Of the 316 implants, there were 70 **implant removals** (22.2%) through 5 years for any reason. Of the 70 implants removed, 55 (78.6%) were removed to treat a complication (see Table 9 below for primary reason for implant removal), and the majority (49 of 70 implants, 70%) were replaced. Of the 237 patients, there were 62 (26.1%) patients through 5 years who had an implant removed. For comparison, at 4 years, 62 (19.6%) implants were removed in the reconstruction patients, with 48 (77.4%) removed due to a complication and 45 (72.6%) replaced.

Table 9: Primary reason for implant removal through 4 and 5 years - R95.

Primary Reason for Removal[1]	**4 Years**[2] **N = 62 Implants Removed**	**5 Years N = 70 Implant Removals**
Capsular Contracture	16 (25.8%)	22 (31.4%)
Patient Choice	14[3] (22.6%)	15[4] (21.1%)
Leakage/Deflation	10[5] (16.1%)	12[6] (17.1%)
Infection	6 (9.7%)	7 (10%)
Wrinkling/Asymmetry/Malposition	7[7] (11.3%)	6[8] (8.6%)
Other	5[9] (8.1%)	4[10] (5.7%)
Implant Extrusion	4 (6.5%)	4 (5.7%)

Notes: [1]In the case where more than one reason for removal was reported, the following hierarchy was used to determine the primary reason: leakage/deflation, infection, implant extrusion, capsular contracture, implant wrinkling, implant palpability/visibility, implant malposition, asymmetry, patient choice to change size/style or to match other side.
[2]As reported in original PMA submission with recategorization of "unknown" primary reason for removal. No new data were added. N of 62 remains the same.
[3]Includes change size/style (12) and remove to match other side (2).
[4]Includes change size/style (12 cases) and remove to match other side (3 cases).
[5]Includes 1 case of "Unknown" as a worst case presentation.
[6]Includes 2 cases of "Unknown" as a worst case presentation.
[7]Includes wrinkling (2 cases), malposition (3 cases), and asymmetry (2 cases).
[8]Includes wrinkling (2 cases), malposition (3 cases), and asymmetry (1 case). Values at 5 years are less than at 4 years due to further clarification of the primary reason for removal and/or data cleaning.
[9]Reported as recurrent carcinoma (2 cases), abnormality on CT scan at mastectomy site (1 case), tissue expansion went poorly due to radiation (1 case), and Ryan procedure (1 case).
[10]Reported as recurrent carcinoma (1 case), abnormality on CT scan at mastectomy site (1 case), tissue expansion went poorly due to radiation (1 case), and second stage breast reconstruction (1 case). Values at 5 years are less than at 4 years due to further clarification of the primary reason for removal and/or data cleaning.

For those patients who underwent **implant revision** (removal with replacement) and had follow-up, the complications of capsular contracture Baker grade III/IV, leakage/deflation, removal, and infection **following implant revision** is summarized in Table 10 below on a by implant basis through 2 and 3 years.

Table 10: Cumulative Kaplan-Meier risk rates of first occurrence of selected complications on a by-implant basis following implant replacement (revision) at 2 and 3 years - R95.

Complication Following Replacement (Revision)	**2-Year Risk Rate**[1] **(95%CI) N = 40 Implants**	**2-Year Risk Rate**[2] **(95%CI) N = 40 Implants**	**3-Year Risk Rate (95% CI) N = 40 Implants**
Capsular Contracture III/IV	32.6% (16.6, 48.5)	27.0% (12.7, 41.3)	33.8% (18.0, 49.5)
Removal/Replacement	25.5% (9.8, 41.3)	23.8% (10.2, 37.5)	26.9% (12.5, 41.2)
Leakage/Deflation	5.3% (0.0, 12.5)	5.2% (0.0, 12.2)	9.5% (0.0, 20.1)
Infection	7.3% (0.0, 17.3)	2.9% (0.0, 8.4)	2.9% (0.0, 8.4)

Notes: [1]As reported in original PMA submission with correction of capsular contracture rate.
[2]Updated 2-year data as reported in 2001 annual report.

With respect to **breast disease**, there were 99 patients of 237 (41.8%) who reported breast disease through 5 years of follow-up. Of these 99 reports, 75 were benign and 24 were malignant. For comparison, as reported in the original PMA submission, there were 31 reports of breast disease through 4 years (11 were benign, 19 were malignant, and 1 was unknown). However, in the 2001 annual report, Inamed indicated that there were 61 additional reports of benign breast disease which were omitted from the original PMA submission, bringing the overall count of benign breast disease to 72 reports through 4 years. Additionally, since year 4, 1 report of breast disease with unknown outcome was recategorized to malignant. Therefore, of the 99 reports of breast disease through 5 years, 7 are actually new reports from year 4.

With respect to **CTD**, there were a total of 5 patients reporting a CTD through 5 years of follow-up. Of these 5 reports, 1 was confirmed (Graves' disease) and 4 were unconfirmed (1 thyroiditis and 3 lupus or RA). For comparison, as reported in the original PMA submission, there were 5 reports of CTD, 1 confirmed and 4 unconfirmed, through 4 years. The number of confirmed and unconfirmed reports remained the same between 4 and 5 years. However, the specific patients constituting the unconfirmed reports changed. Specifically, the data at 5 years reflect the addition of 4 new unconfirmed reports (3 lupus or RA and 1 thyroiditis) and the deletion of 4 unconfirmed reports that were found to be false reports (1 lupus or RA, 1 inflammatory bowel disease, and 2 thyroiditis). Therefore, of the 5 patients reporting CTD through five years, 4 are actually new reports (all unconfirmed) from year 4.

2. Focus Group Study

The ultimate goal of this study was to improve the patient brochure approved in May 2000. An independent study was conducted by Kaplan West Qualitative Research in accordance with the FDA-approved protocol. The focus group study involved 3 augmentation and 3 reconstruction groups consisting of 8-13 women each who have considered, are considering, or have had implants.

The objectives of the independent focus group study were to address issues such as:

- ?? What do women considering implants want to know?
- ?? Does the brochure answer the questions?
- ?? Is it clear and easy to understand?
- ?? Is it appropriate for the lay audience?
- ?? What is the response to the risk information?
- ?? What is the response to the overall layout?
- ?? What are suggestions for improving the booklet?

Some of the key findings from the focus group study were:

- ?? The primary concern is safety.
- ?? Besides safety, women want to know about the implant.
- ?? They want information about the surgery and surgeon.
- ?? They want to know how much it will cost.
- ?? The breadth of information presents the biggest difficulty.
- ?? Women had little interest in reading irrelevant material (suggested separating augmentation and reconstruction information).
- ?? It was hard to follow (suggested glossary, table of contents, etc.)
- ?? The safety tables were appreciated but were confusing to the majority of the women (suggested placing table at the end of the brochure or within the appropriate stratified section, add textual explanations).
- ?? The brochure may be more successful if written more sensitive to the individual reader (reconstruction vs. augmentation patient).

Based on the focus group study, Inamed proposed changes to the patient brochure. However, FDA considered the findings from both Inamed's and Mentor's focus group studies and requested further changes to the patient brochure. The changes were categorized into the primary areas of:

- ?? Add clarification and/or make corrections (lead-ins and contents of safety tables)
- ?? Improve organization/layout (stratify augmentation and reconstruction, position of safety information)
- ?? Make easier to follow (table of contents, glossary, pagination)
- ?? Make easier to read (graphics, fonts, headers)

Inamed incorporated all changes to the patient brochure requested by FDA. FDA considers this condition of approval fulfilled by Inamed.

As a note, Inamed is currently updating their patient brochure, as well as the package insert, to reflect 5-year post-approval study results. Once FDA has finished the review of these two pieces of labeling, Inamed will finalize them for public distribution.

3. Retrieval Study

This study involves a good-faith effort to retrieve explanted breast implants and perform appropriate analyses to determine the mode of failure.

The stepwise approach to the retrieval study analyses is as follows:

- Standard analysis – Visual observations and product disinfection (autoclaved) are performed for all explants received.
- Additional analysis – Extensive visual inspections, leak tests, length measurements of openings, and applicable tests are performed on all implants.
- Mechanical/chemical testing - This testing is not performed if the alleged event is trauma-related, if cause of failure is known, or is based on the interaction between surgery/device/patient. Destructive testing is also not performed if requested by physician or hospital. Otherwise, mechanical testing (shell property and joint) is performed. The need for chemical analysis is made on a case-by-case basis.

Inamed provided a summary of the findings for all explanted devices received between 7/31/00 and 3/31/01. Clinical information and laboratory device observations were recorded. There have been 2458 retrieved implants.

Retrieval Study Summary		**Style 68, Smooth, Round**	**Style 168 Textured, Round**	**Style 163 Textured, Shaped**	**Style 363, Textured, Shaped**	**Style 468, Textured, Shaped**
Total retrieved between 7/31/00 and 3/31/01		569	1415	70	44	360
Clinical (Physician) Observations	Deflation (e.g., partial or complete saline loss)	437	1218	62	34	29
	Non-deflation (e.g., removed for capsular contracture, infection)	97	184	6	6	45
	Intra-operative (e.g., shell puncture during surgery)	29	4	0	2	7
	Clinical term entry in progress	6	9	2	2	13
Laboratory Observations of Device Failure Characteristics[1] [Deflation vs. Non-deflation]	Smooth-edge openings (at crease)[2]	82 (18.8%)	54 (4.4%)	2 (3.2%)	3 (8.8%)	3 (1%)
		1 (1%)	1 (0.5%)	-	-	-
	Sharp-edge openings (not at crease)[2]	132 (30.2%)	969 (79.6%)	51 (82.3%)	21 (61.8%)	191 (64.7%)
		35 (36.1%	67 (36.4%)	-	1 (16.7%)	12 (26.7%)
	Valve delaminations (?50% determined by laboratory)	115 (26.3%)	9 (0.7%)	1 (1.6%)	-	4 (1.4%)
		13 (13.4%)	4 (2.2%)	-	-	1 (2.2%)
	Leaky valves	15 (3.4%)	23 (1.9%)	1 (1.6%)	-	13 (4.4%)
		9 (9.3%)	13 (7.1%)	-	-	2 (4.4%)
	Functional devices (e.g., torn plug strap, partial patch delamination)	66 (15.1%)	162 (13.3%)	6 (9.7%)	10 (29.4%)	83 (28.1%)
		37 (38.1%)	99 (53.8%)	6 (100%)	5 (83.3%)	30 (66.7%)

[1]The laboratory observation rates were stratified between deflated (1st row) and non-deflated devices (2nd row) to make correlation.

[2]If both smooth and sharp-edge openings were observed in an implant, it was counted as a smooth-edge opening.

Mechanical testing was performed on all implants for which the mode of failure could not be determined. The static testing included ultimate break force, ultimate elongation, patch force at failure, and valve force at failure. There was no significant difference in the mechanical results between the deflated and non-deflated devices. This testing did not help determine the mode of failure.

Observed device failure characteristics may represent either a true device failure or be the result of an artifact that may affect the explanted device by the time the device is available for examination (e.g., shipment, excessive handling, autoclaving, method of explantation). Inamed made the following conclusions to date regarding whether a device failure characteristic is representative of a true failure or the result of an artifact:

- ?? Smooth-edge openings are a characteristic frequently seen in retrieved smooth devices. Smooth-edge openings associated with deflation are indicative of a true device failure because they are nearly always associated with deflation complaints.
- ?? Sharp-edge openings were found more frequently in textured implants but are seen in both deflated and non-deflated implants. The reason for these openings is not known. Therefore, sharp-edge openings associated with deflation or non-deflation may be indicative of true device failure or the result of an artifact.
- ?? Percentage of valve delamination is higher for smooth than textured implants. However, it was shown to not have a significant impact on the deflation rates between smooth and textured implants.
- ?? Valve delamination associated with deflation may be a true device failure because they are nearly always associated with deflation complaints.
- ?? Based on the presence of valve delaminations in non-deflated implants, valve delamination associated with non-deflation may be the result of an artifact.
- ?? Leaky valves are most likely the result of an artifact because they are frequently associated with both deflation and non-deflation complaints. More specifically, there were many instances in which the physician reported the device as non-deflated; however, the laboratory found the implant to have a leaky valve. The mode of failure for the leaky valves has not yet been determined.
- ?? Functional devices are most likely an artifact because they are frequently associated with deflation and non-deflation complaints (higher % of non-deflation complaints).

A table below summarizes these true device or artifact findings:

Device Failure Characteristic	Deflated Devices	Non-Deflated Devices
Smooth-edge opening	True device failure	True device failure or artifact
Sharp-edge opening	True device failure or artifact	True device failure or artifact
Valve delamination reported by physician and laboratory	True device failure	Possible artifact
Valve delamination observed by laboratory only	True device failure	Possible artifact
Leaky diaphragm valves	Possible artifact	Possible artifact
Functional	Possible artifact	Possible artifact

The mode of failure for many of the implants were not fully understood (could be device failure or artifact). Inamed made the following conclusions to date regarding the modes of failure:

- ?? The hypothesis regarding the mode of failure leading to smooth-edge opening, a characteristic found more frequently in the smooth implants, is that fold flaw and repetitive abrasion of both sides of the shell create it.
- ?? There is no hypothesis regarding the mode of failure for valve delamination.

FDA expects Inamed to provide a final report of this retrieval study in their next annual report due in July 2002.

4. Fatigue Testing

The purpose of this testing was to determine the fatigue strength of the product line. Fatigue testing was performed with constant displacement equipment (as per the approval protocol) and with new Endura TEC load control equipment. Constant displacement testing was performed at the lower loads (5 and 10 lbs) and load control testing was performed at the higher loads (?20 lbs). Inamed expected the resulting endurance load limit to be above 10 lbs and wanted to use the load control equipment to eliminate imprecision concerns raised by FDA regarding displacement control testing.

Testing was completed on two styles that represented all of their product line – Styles 68 and 168. All test implants were fabricated in standard production. The implants were smallest size (120cc) with the minimum thickness allowed by the design specifications (0.014" for Style 68 and 0.022" for Style 168). The implants were also sterilized prior to testing. Testing was performed at 1 Hz, which is the frequency of loading during walking and avoids undesirable heating at higher frequencies. A minimum of 3 implants for each style was tested for each load value.

Runout (RO) was defined as 6.5M cycles, which was based on 1 step per second for 5 hours per day for 1 year. Although it is not clear why 1 year of life should be considered acceptable, it is also unrealistic that the average person walks for 5 hours a day.

The expected in-vivo load was 5 lbs. This load is based on the assumption that the worst case is a breast of a lactating women (800 g or 1.8 lbs), which also correlates to the largest size implant of 800cc. Taking into consideration the motion of the breast during a running step, the force on the breast was determined to be 3.6 lbs, which was then rounded to 5 lbs. The acceptance criteria for each style were then defined as: (1) 100% RO to 6.5M cycles at in-vivo load (i.e., 5 lbs); (2) 100% RO at twice the in-vivo load (i.e., 10 lbs); and (3) evidence that the in-vivo load is past the inflection point of the AF/N curve.

The results were:

	STYLE 68 Smooth, Round, 120cc	**STYLE 168 BIOCELL? Textured, Round, 120cc**
Ultimate Static Force[1]	1638 lbs	1963 lbs
Endurance Load Limit at 6.5M cycles RO[2]	20 lbs	20 lbs

[1]Implant fails at static forces greater than those expected during mammography (55 lbs) or to cause rib fracture (1340 lbs).

[2]The endurance load limit for both styles is somewhere between 20 and 30 lbs; however, for worst case purposes, it will be considered 20 lbs.

The acceptance criteria for the fatigue testing were met. FDA considers this condition of approval fulfilled by Inamed.

5. Shelf Life Testing

The purpose of this testing is to support a 5-year expiration date on the package label. Inamed is allowed to use their existing 4-year expiration date while this testing is being completed. Testing will be performed at baseline (year 0) and then at 1, 2, 3, 4, and 5 years on representative Styles 68 and 168.

A report of the year-zero results was provided. The results were as follows:

Test	Results
Shipping Simulation Inspection	Pass
Thermoform Dye Penetration	Pass
Fill Tube Pouch Integrity	Pass
Thermoform Peel Strength	Pass
Patched Shell Leak Inspection	Pass
Patch Joint Integrity	Pass
Valve Joint Integrity	Pass
Valve Failure Force	Pass
Shell Ultimate Break Force	Pass
Shell Ultimate Elongation	Pass
Shell Tear Force	Pass
Shell Tensile Set	Pass
Fill Tip Removal Force	Pass

FDA expects Inamed to provide an updated report each year until a 5-year expiration date is supported.